REMARKS

Formal Matters

This paper is responsive to the Office Action dated June 3, 2003, which is the second Action on the merits of the application.

Claims 31-50 and 52-81 are under examination, and stand variously rejected.

No claims are canceled, added, or amended in this application.

Reconsideration and allowance of the application is respectfully requested.

Interview:

The applicants wish to thank Examiners Christopher Yaen and Gary Nickol for a helpful telephone interview with Carol Francis and Michael Schiff on November 24, 2003. Arguments presented during the interview are incorporated into this Response.

Applicants gratefully acknowledge withdrawal of the previous rejections made under 35 USC § 112 ¶ 2, and the rejection under § 102 with respect to the Kimura reference.

Rejection under 35 USC § 112 ¶ 1:

Claims 31-50 and 52-78 are rejected under the enablement requirements of § 112 ¶ 1. The Office Action indicates that the specification is enabling for the making of the invention. However, it questions whether the specification enables the use of the claimed invention, on the assertion that the use of a cancer cell expressing a recombinant cytokine fused on its surface has not been taught.

Applicants respectfully disagree.

The specification provides an extensive review of the use of cytokine-secreting tumor cells as part of an immunogenic composition. See, for example, page 8, lines 1-21.

Furthermore, *the application as filed contains working examples.* In Example 5, animals were vaccinated with the T9 glioblastoma tumor cell line, transfected to express either the secreted or membrane form of M-CSF. The animals were subsequently resistant to challenges with the parental (untransformed) T9 cell line, attributable at least in part to a vigorous T lymphocyte anti-tumor immunity.

Accompanying this response are the following publications:

- Turner et al., Hu. Gene Ther. 9:1121-1130, 1998. This publication reports experiments done with MPC11 melanoma line in BALB/c mice. Fig. 4 shows the protective effect for animals immunized with irradiated MPC11 cells, in combination with a mouse fibroblast cell line (3T3 cells) genetically altered to secrete GM-CSF.

- Borrello et al., Hu. Gene Ther. 10:1983-1001, 1999. This publication teaches the efficacy of a vaccine according to the claimed invention in BALB/c mice having reestablished tumors made with the A20WT line. Animals subsequently immunized with irradiated A20WT cells in combination with a cell line engineered to secrete GM-CSF (B781GM-CSF) showed better incidence of tumor-free survival than animals immunized with irradiated tumor cells alone (Fig. 6).

- Luznik et al., Blood 101:1645-1652, 2003. This publication reports that a GM-CSF secreting cell line in combination with autologous mammary carcinoma tumor cells was able to reduce metastatic cancer.

- Yei et al., Gene Ther. 9:1302-1311, 2002. Figure 7 shows that C57BL/6 mice having a reestablished tumor survived better and had a smaller rate of tumor growth if the GM-CSF cytokine was in the *membrane-bound* form rather than in the secreted form.

Currently, the idea of using autologous cells genetically modified *ex vivo* to produce secreted cytokine is a product of Cell Genesys, a publicly traded company with a market capitalization of about $544 million. Accompanying this Response is an excerpt from the company's website (www.cellgenesys.com), showing the success of the Gvax® product in clinical trials for four different cancers.

All this evidence produced since the filing of this application shows that the use of cytokine-producing cells in a cancer vaccine is a promising technology.

Withdrawal of this rejection is respectfully requested.

Rejection under 35 USC § 112 ¶ 2:.

The claims stand newly rejected under § 112 ¶ 2 with respect to the indication in the claims that the cells are *inactivated.*

Definition and exemplification of what is meant by inactivation is provided in the specification on page 20, lines 5-10. As is evident from the specification, all that is required for a cell to be "inactivated" is that the cell be rendered incapable of cell division to form progeny. The cell may or may not have other capabilities, as long as it meets the primary requirement of the definition. This accords with the standard meaning of the term to those skilled in the art.

Accordingly, the term is definite, and the claims comply with the requirements of § 112 ¶ 2. Withdrawal of this rejection is respectfully requested.

Rejections under §102(a) and §103(c):

Jadus et al.

Certain claims in the application stand rejected under 35 USC § 102(a) or alternatively under § 103(a) with respect to the publication by Jadus et al., Blood 87:5232, 1996.

Applicants respectfully disagree. First, as previously explained, this reference does not qualify as § 102(a) prior art. The scientists in the Jadus group and the inventors on this patent application collaborated at U.C. Irvine in the preparation of some of the reagents used. The present Office Action indicates that the Jadus publication is an invention "by another", simply because the authorship is different from the inventorship in this patent application. But this is not the analysis required by the law. The question is *who actually invented* the relevant aspects of what is disclosed in the cited reference. *In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1982). Applicant can rebut a prior art challenge under § 102(a) by showing reference's disclosure was derived from applicant's own work. MPEP § 2132.01.

Secondly, the article differs from the claimed invention on a substantive basis. The purpose of the article is to determine what effect the presence of M-CSF on a tumor cell has on the ability of the cells to be recognized by macrophages. They found that macrophages killed hybridoma cells or T9 glioma cells directly (Figure 7), by binding M-CSF through receptors on

the macrophage surface. This does not constitute administration of cytokine expressing cells to a subject. Instead, the cytokine expressing cells are used as *target cells* in a tissue culture experiment. Since the reaction consists of macrophages directly attacking target cells, it does not constitute an immunological response.

The Office Action states that Jadus at page 5239, col. 1, "points the applicant in the direction of the instant invention" (Office Action page 6, second paragraph). In fact, what the excerpt refers to suggests that "injection of the mM-CSF retrovirus *directly into a tumor*. . . may induce the endogenous macrophages to kill those infected tumor cells and perhaps reduce the tumor burden. [The macrophages may then] act as antigen presenting cells and then stimulat[e] systemic immune responses." (emphasis added)

Jadus thus actually teaches against what is claimed in this application, and directs the reader to an entirely different course of action. Specifically, the reader is being directed to inject the tumor *in vivo* with a M-CSF retrovirus expression vector in order to provide for expression M-CSF *in the tumor cell*— a form of *gene therapy*.

In view of the above, Jadus neither anticipates nor renders obvious the claimed invention. Applicants respectfully request that the rejections based on Jadus under §102(a) and §103(c) be withdrawn.

Tuck et al.

Certain claims stand rejected under 35 USC § 102(a) as being anticipated by Tuck et al. *Blood* 84:2182-8, 1994. The Office previously indicated that Tuck et al. teach a COS-1 cell expressing a M-CSF cytokine, which can be either membrane associated or soluble in its natural form.

Applicants respectfully disagree. Tuck et al. describe *in vitro* studies of M-CSF expression of cells in culture, with a view to characterizing the protein isotypes that are formed, and where they are located in the cell. There is no suggestion to combine the M-CSF expressing cells with a pharmaceutical excipient, or to make any of the cell preparations while taking the precautions needed to obtain a composition that is adequately sterile, sufficiently free of contaminants, and otherwise formulated for human administration. In contrast, Example 5 of the specification shows how membrane M-CSF expressing cells limit tumor growth, increase

survival, and protect against rechallenge (page 61 ff.). Pages 32-34, 38-41, and 66-68 provide detailed information on the formulation, testing, and use of cytokine secreting cells in human administration.

The current Office Action indicates that the product taught by Tuck et al. is not constrained with respect to its intended use. However, this does not affect the patentability of the pending claims in this application. Claim 31 explicitly indicates and limits coverage to compositions containing a *pharmaceutical excipient* and *formulated for human administration.* These explicit features are not taught in the Tuck reference.

Applicants respectfully request that the rejection based on Tuck under §102(a) be withdrawn.

Accordingly, the claimed invention is patentable over the cited reference. Withdrawal of all prior art rejections is respectfully requested.

Terminal Disclaimer:

Without intending any admission as to the relationship between the subject matter claimed in the present application and that in U.S. Patent No. 6,277,368, to which this application claims priority, enclosed herewith is a Terminal Disclaimer, disclaiming any portion of the term otherwise entitled to this application that exceeds the term of U.S. Patent No. 6,277,368.

Conclusion

Applicants respectfully request that all outstanding rejections be reconsidered and withdrawn.

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number IRVN-001DIV.

Respectfully submitted,
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Date: March 12, 2004

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Enclosures: Turner et al., Hu. Gene Ther. 9:1121-1130, 1998
Borrello et al., Hu. Gene Ther. 10:1983-1001, 1999
Luznik et al., Blood 101:1645-1652, 2003
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